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Discussion: Is the FDA in need of a major change in the way it regulates?

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It is important for a regulator to carefully balance sometimes conflicting concerns: protecting the public; ensuring that drug and devices development remains viable, also economically; keeping up with scientific developments and breakthroughs, emerging new methods, and changing insight.

While it is necessary beyond question to have crystal clear procedures in place, this does not mean that every aspect of the regulatory framework should be time invariant. For example, when in one of the relatively early phase of the AIDS epidemic co-enrollment appeared on stage, partly forced by patients' rights group, and against what regulators, academic researchers, and industry considered wise, it turned out to be a very beneficial device. While co-enrollment challenged an until then seemingly foundational aspect of a clinical trial used for drug approval, and while it raised a number of complex methodological issues, it is partly to be credited for the development of highly active anti-retrovirus therapies.

What is needed is clear mechanisms to continually examine the need for change and then procedures to implement such change. If rules are conceived "for eternity," the consequence is that no agreed upon mechanisms would exist regarding change. It is an illusion though that change can be kept out of the door and thus, when it inevitable happens, adjustments and changes would be governed by *ad hoc* procedures—precisely the reverse of what is intended. In other words, change and evolution should be "domesticated."

Evidently, this cannot be done within the regulators' community alone, but should rather be done in concertation with the research communities in industry and academia, as well as with other stakeholders, in particular patients, payers, etc.

It is fair to say that change happens all the time, and over recent decades regulators worldwide have contributed to structures that feel the pulse of changing evolutions and new developments. For example, joint conferences, *ad hoc* and on a regular basis, between regulators, academia, and industry are being held to the benefit of furthering insight. I would like to refer to workshops involving FDA and industry, European Medicines Agency (EMA) and the Drug Information Association (DIA), etc. Some of these are organized in conjunction with further partners such as the American Statistical Association (ASA), the Society for Clinical Trials (SCT), the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI), etc.

Another important vehicle is working parties and hearings on particular topics. I will mention a few.

The FDA commissioned a project, under the auspices of the National Research Council and headed by Rod Little, that led to the 2010 report on *Prevention and Treatment of Missing Data in Clinical Trials.* Working party members held current and past positions in all three sectors (academia, industry,

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regulatory). Also, they came from various backgrounds within statistics and clinical trials (for example, some are experts in survey sampling, allowing for fruitful cross-sub-discipline symbiosis). Representatives from different and sometimes competing schools of thought partook. While the FDA took the initiative and, at properly organized points in time during the process they could state their expectations and feedback could be exchanged, the working party was entirely independent.

The EMA has organized hearings on such topics as subgroup analysis. This allows input from the broader research communities, stakeholders in the topic and in different but related topics (e.g., orphan diseases), industry, and fellow regulators.

A structure not yet mentioned but extremely important is the International Conference on Harmonization (ICH). A large majority of the issues of importance to a regulatory body are not confined to that body alone, but is of international significance. An example is the recent revision of the ICH-E9 on the statistical principles for clinical trials, where regulators and other stakeholders from the USA, Europe and Japan have collaborated.

A related international initiative is the recent working group on the concept of estimands. It is a simple but sometimes forgotten truth that discussing estimators, procedures, etc. is rather pointless if one has not reflected on what is being estimated. It is therefore a crucial endeavor to clearly define concepts and language, and assess how this can enhance drug development and the practice of clinical trials. A successful outcome of this project will be transforming in a number of areas. To give one example, sensitivity analysis regarding missing data can be harnessed better so that, routinely, a sensitivity analysis will encompass different estimators, under differing assumptions, but for the same estimands.

Evidently, many scientific evolutions that are taking place right now and undoubtedly will in the future, will make the need for initiatives like the ones described above more needed than ever. Some evolutions are broad and general, such as big data and data science. Without engaging here in a discussion as to what they now really mean, it is important to assess sooner rather than later what the implications are for drug development, for the regulatory framework, and for the regulators.

Other evolutions are more directly relevant for medicine, clinical practice, and hence for regulators. A key example is personalized medicine. I think it is a nice example to underscore just how much collaboration is needed. While scientific research is not the exclusive right of academic and other research institutions, it seems fair to say that there are important and highly technical research efforts needed, that go beyond what regulators and industry want to allocate their resources to. At the same time, there is a risk, when research is solely done in an academic environment, that "mathematization" goes in the direction of ever more abstract and ever more general frameworks, that somewhat lose attraction to and relevance for biopharmaceutical development. Hence, joint projects, ideally co-sponsored between granting bodies, industry, and/or regulators, should be given a prominent place.

So, all in all, it seems that a good number of initiatives have been taken in the past, to ensure modernization of thinking and embracing of emerging concepts and tools. However, many of these are still of an *ad hoc* nature. It appears important to structurally organize the consultation and learning processes as much as possible, while indeed leaving room for spontaneous initiatives as well. On a regular basis, and following a clear but flexible protocol, it would seem important to identify areas where development and consultation is needed. Following this, there should be procedures to then identify to best achieve a particular goal, where a number of choices need to be considered. Without being complete, these would include:

- Regulators to involve: FDA, EMA, Japan, ICH, others,…
- Other stakeholders to involve:
    - Academia and research institutions (if so, what disciplines)
    - Industry

    - Patients
    - Payers, insurance companies,…
    - …
- Funding (internal funding, external resources, funding agencies, etc.)

In conclusion, regulators should regulate how their own organization learns and transforms, in an orderly and stable fashion, easy to audit and very transparent, and in concertation with all relevant stakeholders, whilst at the same time strictly maintaining its independence. The latter means that the ultimate decision to change a procedure or adopt a new one is strictly with the regulator, and with the regulator only.

A key requirement is that agencies like the FDA should be scientifically strong and independent, with a clearly defined mission and shielded from overly strong political and economic influences. In spite of their long standing, they may be too vulnerable at this time. Clear checks and balances in this respect are crucial.

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